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# *Biogenerics & India*

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# Biologics - Background

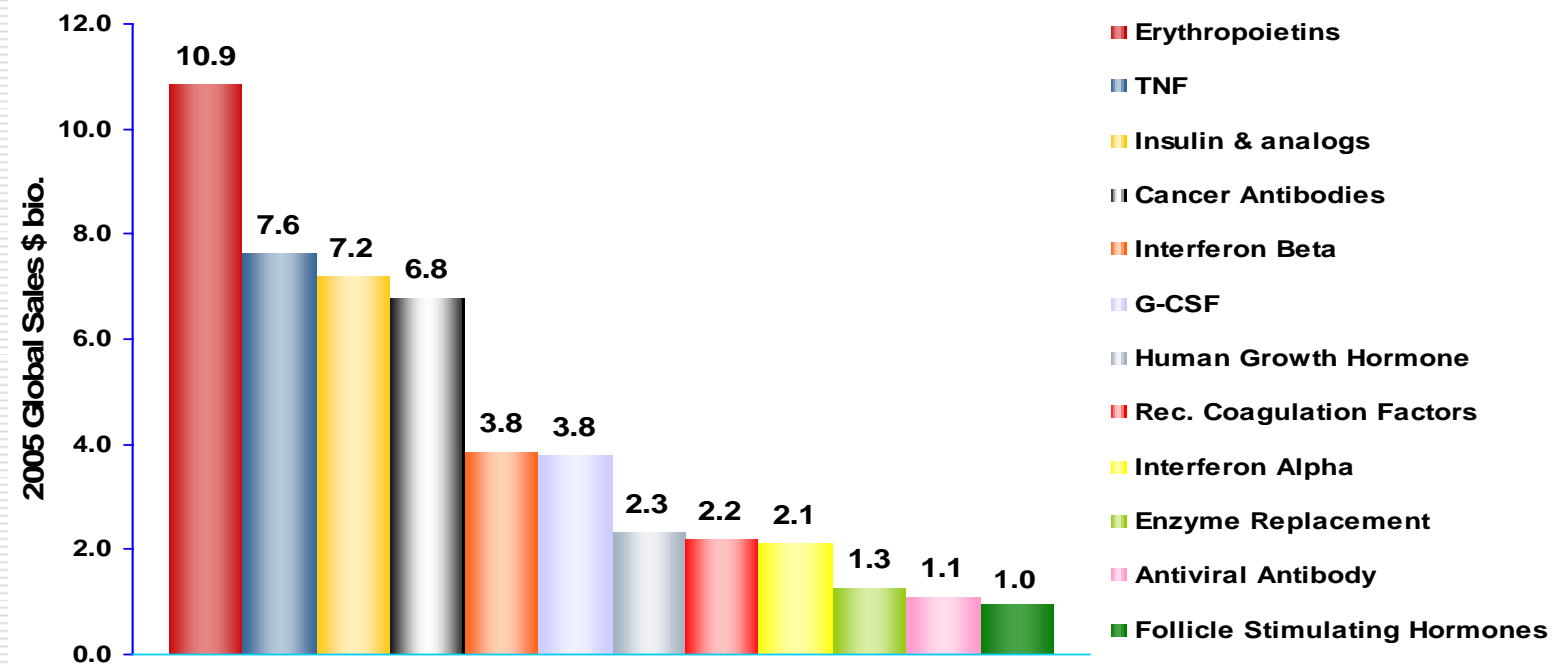
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- ❑ Global biologics market is estimated to be ~\$ 53 billion (excluding vaccines) constituting ~9% of global pharmaceutical market.
- ❑ ~125 biologics currently marketed.
- ❑ The research and development costs associated with biologics are high because biologics are structurally complex and difficult to manufacture.
- ❑ Genentech, estimated that it has invested \$6.4 billion in research over the last 28 years.
- ❑ These high costs are then passed on to consumers, who often foot bills for biologic treatments ranging anywhere from \$10,000 to \$25,000 a year. In some rare cases, costs can exceed \$170,000 per year.





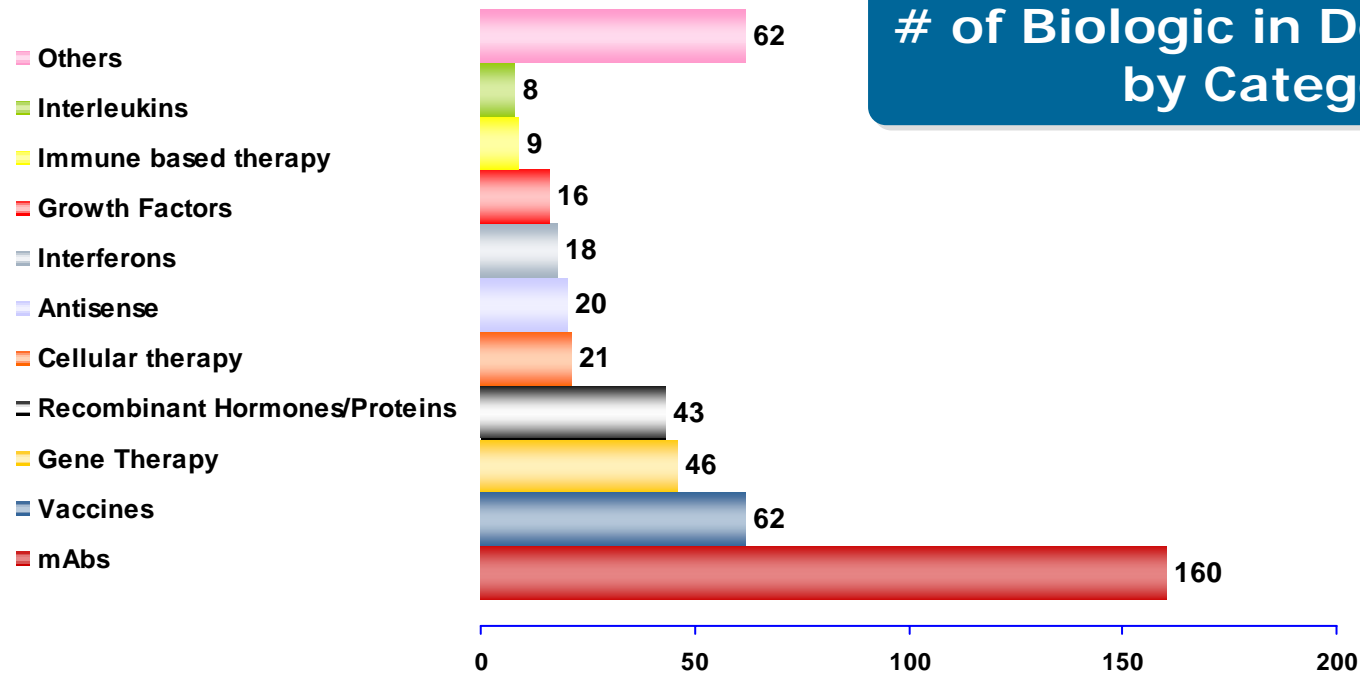
# Erythropoietin is the leading class of biologic constituting ~22% of biologic market (excl. vaccines)



## Leading Biotech Products

Product	Compound	Company	2005 ww Sales (\$ bio.)*	Growth (YOY) %
neulasta /neupogen	PEG/FILGRASTIM	AMGEN	3.50	31.5%
mabthera/ rituxan	Rituximab	ROCHE/GENE NTECH	3.33	22.0%
procrit/ eprex	Epoetin alfa	j&j	3.32	-7.0%
aranesp	Darbepoietin alfa	AMGEN	3.27	32.0%
enbrel	Etanercept	AMGEN	2.57	42.0%
remicade	Infliximab	j&j	2.54	18.0%
epogen	Epoetin alfa	AMGEN	2.46	-6.0%
neorecormon, epogin	Epoetin beta	ROCHE	1.81	8.0%
herceptin	Trastuzumab	ROCHE	1.72	48.0%
avonex	Interferon beta-1a	BIOGEN IDEC	1.54	8.90%
TOTAL OF TOP 10			26.07	

# Monoclonal antibodies, gene therapy are constitute major proportion of biologic pipeline apart from vaccines



• >400 biologics in development constituting ~19% of all developments are biotech products

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# BioGenerics

**The biogenerics market is tipped to reach \$16bn (€11.9bn) by 2011.**

**Regulated markets are taking the next step for biosimilars. ROW countries could act as a launch pad taking products subsequently to regulated markets.**

# Differences between Chemical Entities and Biogenerics

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<b>Chemical entities</b>	<b>Biogenerics</b>
<ul style="list-style-type: none"><li data-bbox="293 667 1113 863">❑ Well-defined, easy-to-characterize molecular structures with impurity profiles that depend on their synthetic route of manufacture</li><li data-bbox="293 948 1113 1043">❑ In vivo safety and efficacy are unrelated to product origin</li></ul>	<ul style="list-style-type: none"><li data-bbox="1153 667 1973 815">❑ Routine chemical analysis are not sufficient to compare a biogeneric to its originator product</li><li data-bbox="1153 895 1973 1193">❑ The demonstration of approvability for biogeneric differs from the standard generics approach as it is based on a comparability exercise rather than on demonstration of bioequivalence</li><li data-bbox="1153 1278 1973 1369">❑ Need to establish on a case by case basis.</li></ul>

# A tentative classification of biological therapeutics

<b>Class</b>	<b>Example</b>
<b>Biotech products</b>	recombinant DNA technology; controlled expression of genes coding for biologically active proteins in prokaryotes and eukaryotes including transformed mammalian cells; hybridoma and monoclonal antibody methods
<b>Vaccines</b>	vaccines
<b>Blood derivatives</b>	sera; immunoglobulins; coagulation factors; plasma; albumin; interleukins
<b>Other products extracted from native (non-engineered) biological sources</b>	insulin; heparin and derivatives; amino acids; antibiotics obtained through fermentation; hyaluronic acid

# Biogeneric - Market Outlook

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- ❑ 13 of the leading biologics achieved mega-blockbuster status (i.e., exceeded \$2 billion in global sales).
- ❑ Those biologics that lose patent protection open an emerging opportunity for biogenerics.
- ❑ Taking a global perspective, we see that a branded biologic priced at \$10,000 a year may cost just \$2,000 to manufacture in the U.S. or Europe.
- ❑ The high prices of biologic therapies make it imperative that generic or off-patent products be marketed as options for consumers after patent and exclusivity protections for manufacturers have expired.
- ❑ Europe is leading the biogeneric charge; seven biosimilars have launched there and four more were recently approved.

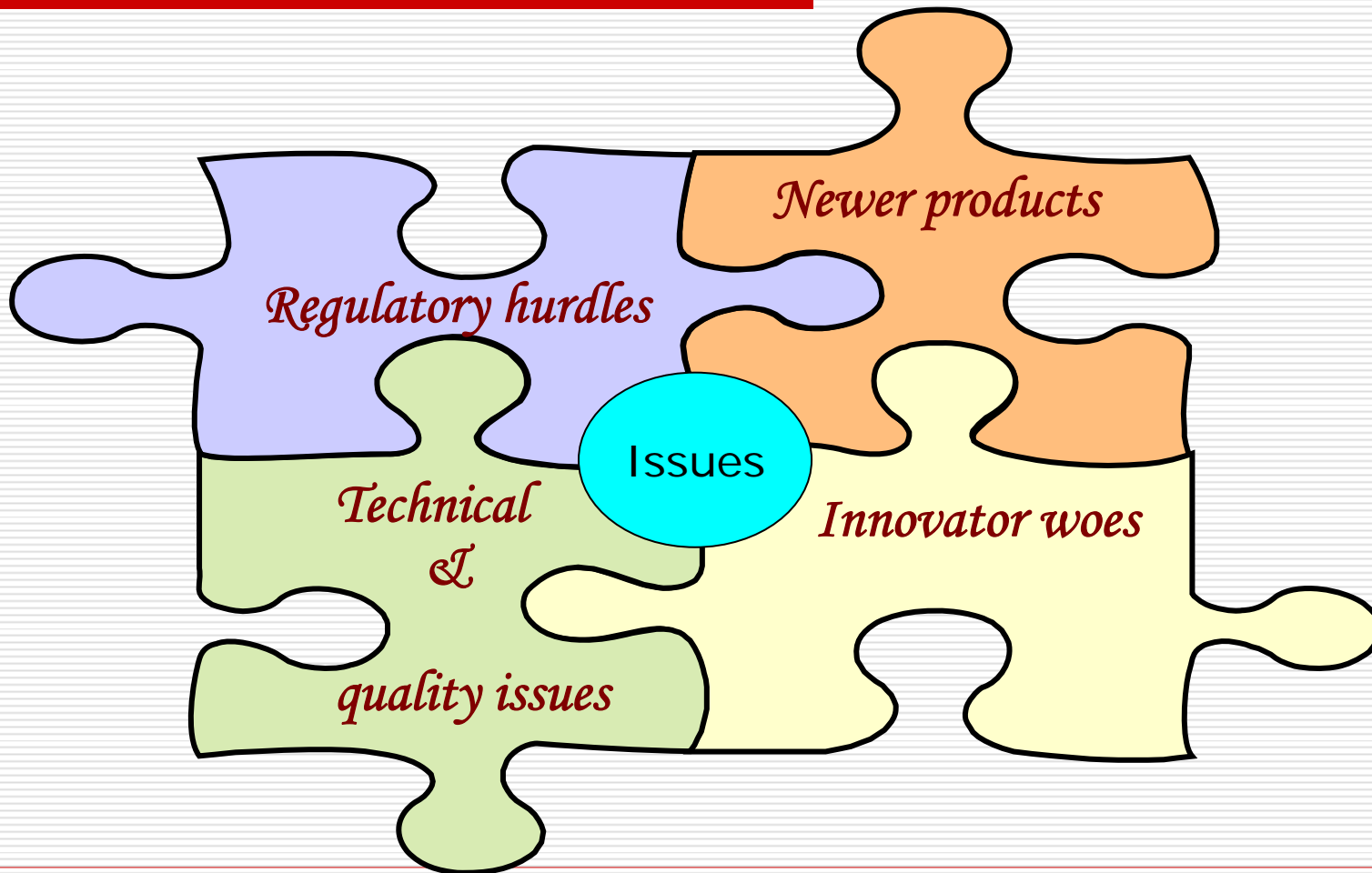
# Biogeneric - Market Outlook

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- Worldwide interest in biogenerics is gaining momentum and is expected to reach \$5.8 billion by 2012.
- By 2013, at least 10 branded biologics with total sales of \$15 billion will be generic and prime targets for genericization.
- But first such stumbling blocks as safety, access to innovators' key intermediates, process controls, availability and access to bulk materials, specifically designed and adapted analytical procedures and validation studies must be addressed.
- Also, biosimilars cannot currently be marketed in the US because there is no pathway for them to reach the market.

# Issues surrounding Biogenerics

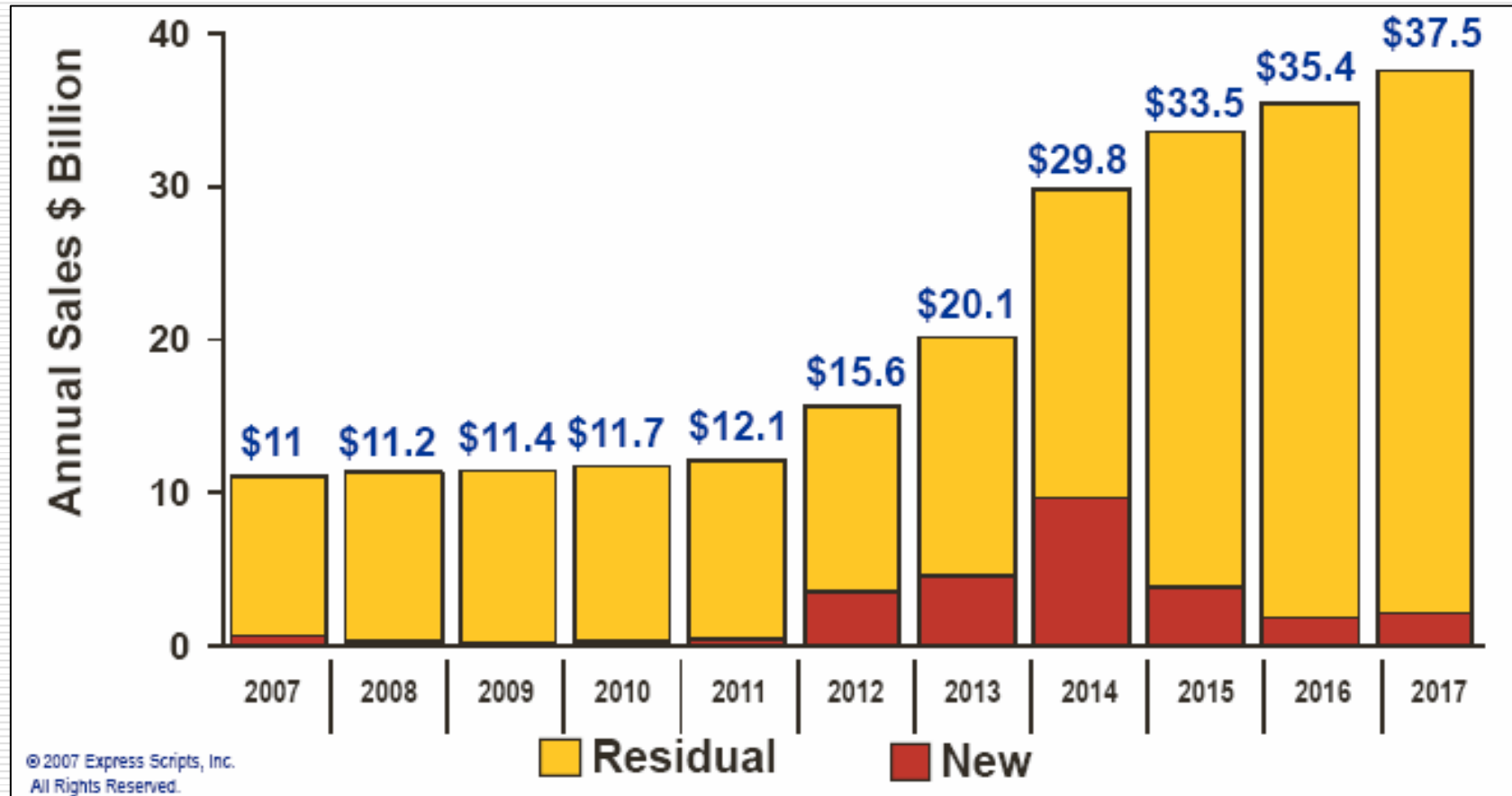
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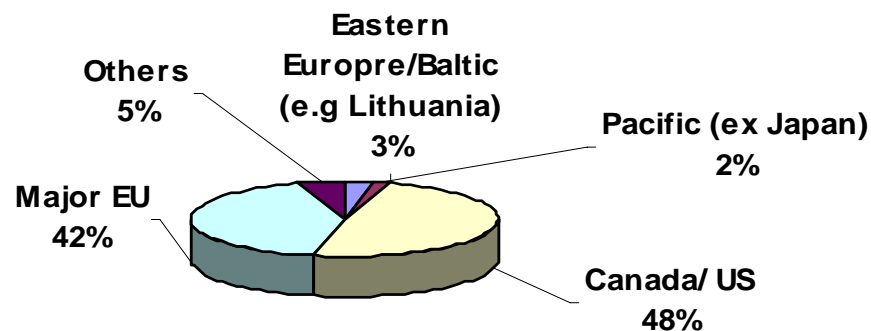
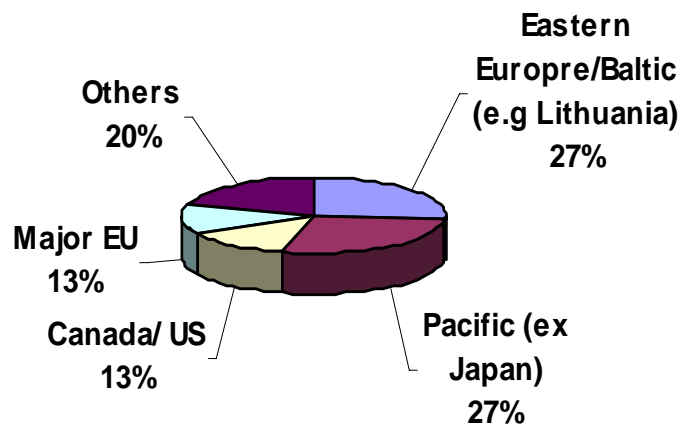
## Selected biologics with expired patent

Product	Compound	Company	Expired
Filgrastim	GM-CSF	Amgen	2007
Engerix-B	Hepatitis B Vaccine	GSK	2006
Neupogen	G-CSF	Amgen	2006
Novolin	Human Insulin	NovoNordisk	2005
Protropin	Growth hormone	Genentech	2005
Activase	t-PA	Genentech/BI	2005
Epogen, Procrit	EPO- $\alpha$	Amgen/J&J/Sankyo	2004
Nutropin	Growth Hormone	Genentech	2003
Humatrope	Growth Hormone	Eli Lilly	2003
Avonex	Interferon b1a	Biogen	2003
Intron A	Interferon a2b	Schering Plough	2002
Humulin	Human Insulin	Eli Lilly	2001

# Biologic Drugs Losing Patent Protection



# Markets in which Biogenerics are currently marketed



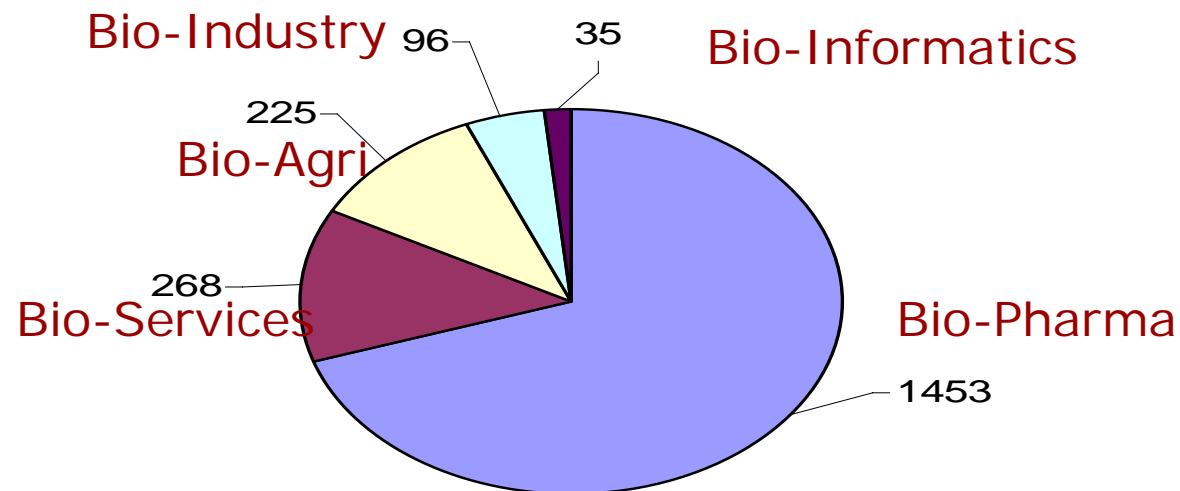
## Markets in which pipeline biosimilars are being targeted towards

## Leading Generic Companies & their biogenerics portfolio

Company	EPO	CSF	Insulin	HGH	INF	tPA	mAB	Total
Teva/Sicor/B TG	D	M		M	M			4
Sandoz				M				1
Pliva (+Mayne)	M	D	M					3
Stada	D	D			D			3
BioPartners/ LGLS	M	M	M	M	M			5
BioGenerix	D	D						2
GeneMedix	D	M			D		D	4
Dragon	M							1
Biocon	D	M	M	D	D	D	D	7
Scino Pharma	D		D	D	D		D	5
Scigen			M	M	M	D	D	5
Wockhardt	M	D	M		D			4
DRL	D	M					D	3
Shantha Biotech	M			D	M	M	D	5
<b>Total</b>	<b>12</b>	<b>9</b>	<b>6</b>	<b>7</b>	<b>9</b>	<b>3</b>	<b>6</b>	<b>52</b>

# Indian Biotechnology Market

- ❑ The Indian biotech market has doubled in size in the past two years, reaching a value of US\$ 2.08 billion in 2006-07, compared to US\$ 1.45 billion in 2005-06.
- ❑ The Indian market currently accounts for a little over 1.1 per cent of the global biotech market.
- ❑ Off the 50 odd biotech products 13 are available in India & 7 biotech drugs are indigenously developed and produced by Indian Companies.



**Biotech Industry Revenues - 2006-07 (US\$ million)**

# Biogenerics - India

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- Companies in Indian generics universe have gross margins closer to 50%. This means that an Indian generics company could enter the market, manufacture the same product, and be content to sell it at \$4,000-5,000, a 50–60% discount.

For example, last year Dr. Reddy's launched a Biogeneric version of Roche's Rituxan/Mabthera in the Indian market at Rs. 20,000 per vial, or approximately \$505, a 50% discount to Roche's price in India.

- With additional entrants and lower-cost manufacturing, prices could be driven down further. For example, Wockhardt recently invested \$38 million to build a facility capable of manufacturing 15% of the worldwide supply of biologics.
- Major brands of Erythropoietin products have become key targets for biogenerics, after accounting for 18.7% (\$12bn) of global pharmaceutical sales in 2006. Amgen's Aranesp held 55% of the EPO market in 2006, typifying the rapid growth of long-acting products.

*"All the biotech products produced by Indian companies are generic in nature.  
India has a huge market potential for Biogenerics".*

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- ❑ Off the 50 odd biotech drugs 13 are available in India and seven biotech drugs are indigenously developed and produced by the Indian companies.
- ❑ Typically the market potential in India for biogenerics has been in the range of 0.1 percent (EPO) to 0.2 percent of (Insulin) of the global market value based on the type and class of molecule.
- ❑ India has over 130 home grown biopharmaceutical companies, many of which are fully integrated.
- ❑ The global market for Indian Biopharmaceutical companies have touched \$ 1.5 Billion in revenues (2006) with CAGR of 27%.

*Indian biogeneric companies on the threshold of globalization, 2007 (biospectrum)*

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# Factors Driving Development of a Biogenerics Market

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- ❑ Multiple Patent expiries for biologics launched in the late 1980s/ early 1990s.
- ❑ Considerable market size for these biologic products.
- ❑ Technological advancements enabling 'replication' of biologic products.
- ❑ Consumer interest in lower cost alternative to expensive branded biologics.

**Biogenerics are becoming technologically feasible and economically necessary, therefore are gaining Regulatory and Political attention**

# Key advantages

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- At present India is one of the major contributors in the world biogeneric market along with the china. Some of the that India has upon other countries in biogenerics are-
  - ✓ Highest number of US FDA approved plants outside the US.
  - ✓ Compliance with GCP guidelines is an rise with Indian Companies.
  - ✓ Highly qualified human resource availability.
  - ✓ Low capital and operational cost.
  - ✓ Pharma sector highly competitive in bioprocessing skills.
  - ✓ Excellent genomic research opportunity.

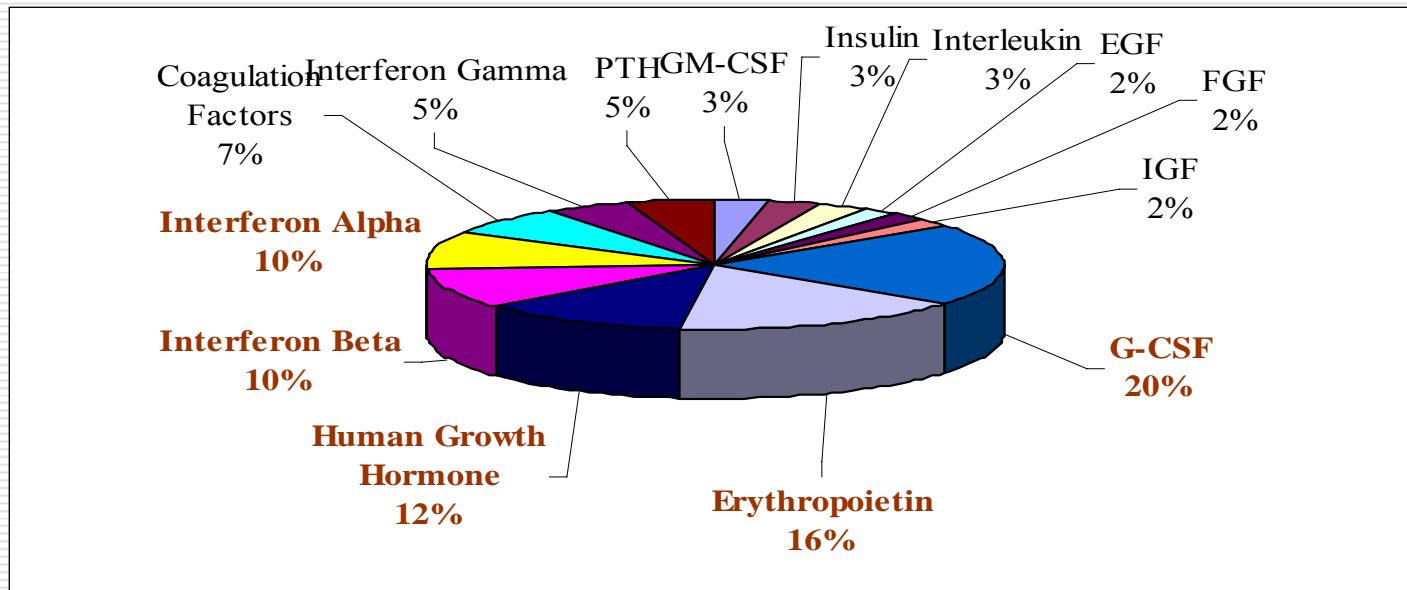
# Measures that are fueling rapid growth

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- ❑ Increase in partly public-funded biotechnology incubators and parks.
- ❑ Increase in the private venture capital, fiscal incentives and tax benefits for R&D and exports.
- ❑ Streamlining of regulatory pathway and reduction in the approval time by various regulatory agencies.
- ❑ Active role of Indian Pharmacopoeia in issuing product specific monographs.
- ❑ Increased penetration of private health insurance.
- ❑ Increase in the burden of diseases (especially lifestyle diseases).
- ❑ Increase in per capita pharmaceutical spend.
- ❑ Modernization and integration of patents and other intellectual-property offices with adoption of electronic filing system.

# Protein Classes in which biogenerics are in development

- **Biogenic Development has extended into protein classes with high market potential.**



Biogenic companies do not focus on providing merely copies of existing drugs, they try to improve manufacturing processes.

# Target Biologics Market Share & Patent Status

Biologic	Leading Brand	Company	Launch Year	Patent Expiry		Worldwide Sales 2006 (USD bn)	sales 2010 (USD Mn) EU Market
				US	EU		
Erythropoietin Epointin alpha and beta	Eprex/Procrit, Epogen, Epogin/Neo Recormon	J&J, Amgen, Roche	1988 (alpha), 1990 (beta)	2014 (alpha), n/a (beta)	Expired (alpha & beta)	13	701
G-CSF	Neupogen	Amgen	1991	2008	Expired	5.6	605
Interferon alpha	Intron, Roferon	Schering Plough, Roche	1987	Expired	Expired	2.3	188 (EU+US)
Interferon beta	Avonex, Rebif, Betaferon	Biogen Idec, Serono	1996 (1a) 1993(1b)	2008-2013 (1a) Expired(1b)	2012 (1a) Expired (1b)	3.7	131
Human growth hormone	Genotropin, Norditropin, Humantropin and others	Pfizer, Novo Nordisk, Lilly and Others	1988	Expired	Expired	1.9	442 (EU+US)

# Biogeneric Manufacturers and Their Products

Company	Launched Biosimilars	In the Pipeline
Barr	EPO scheduled for launch in Eastern Europe	G-CSF (Filgastrim), Insulin, and HGH
Biocon	Insugen (Insulin in India and China), Erypro (EPO) G-CSF, Nimotruzumab, BIOMAb EGFR	Insulin, glargine and HGH
Biopartners	Valtropin (rHGH)	Alpheon (INF- $\alpha$ ) and EPO
Cipla	None	Autoimmune, cancer and cardiovascular
Dr. Reddy's	G-CSF (Filgastrim)	Nine (9) development
Glenmark	None	GBR 500 (mAb for MS), GBR600 (antithrombotic) and mAbs for adhesion molecular inhibitors
Intas Biopharma	Neukine (G-CSF), Erykine (EPO) and Intalfa (INF-alpha2b)	Six (6) development programs
Prolong Pharmaceuticals	None	PEG-EPO and other PEGylated proteins

## Biogeneric Manufacturers and Their Products

<b>Company</b>	<b>Launched Biosimilars</b>	<b>In the Pipeline</b>
Ranbaxy	Nugraf (Filgrastim), Macrogen (Molgramostim from Zenotech)	mAbs in oncology and neurology
Sandoz	Omnitrope (HGH), Binocrit (EPO)	Six (6) development programs including G-CSF (Filgrastim)
Shanta Biotechnics	Shaferon (INF-alpha2b, Shankinase (streptokinase) and Shanpoietin (EPO)	mAbs and PEGylated therapeutic proteins
Stada	EPO-Zeta (approved)	Filgrastim
Teva	G-CSF (Filagstrim), Teva-Tropin (HGH), INF-alpha2b	Insulin, EPO and interleukins
Wockhardt	Wepo (EPO), Wosulin (insulin) INF-alpha2b, G-CSF	Insulin Glargine

*These companies have already introduced as many as seven biotech drugs (Hepatitis B vaccine, Streptokinase, Insulin, G-CSF, Erythropoietin, Human Growth Hormone and Interferon alpha 2b) under many brands.*

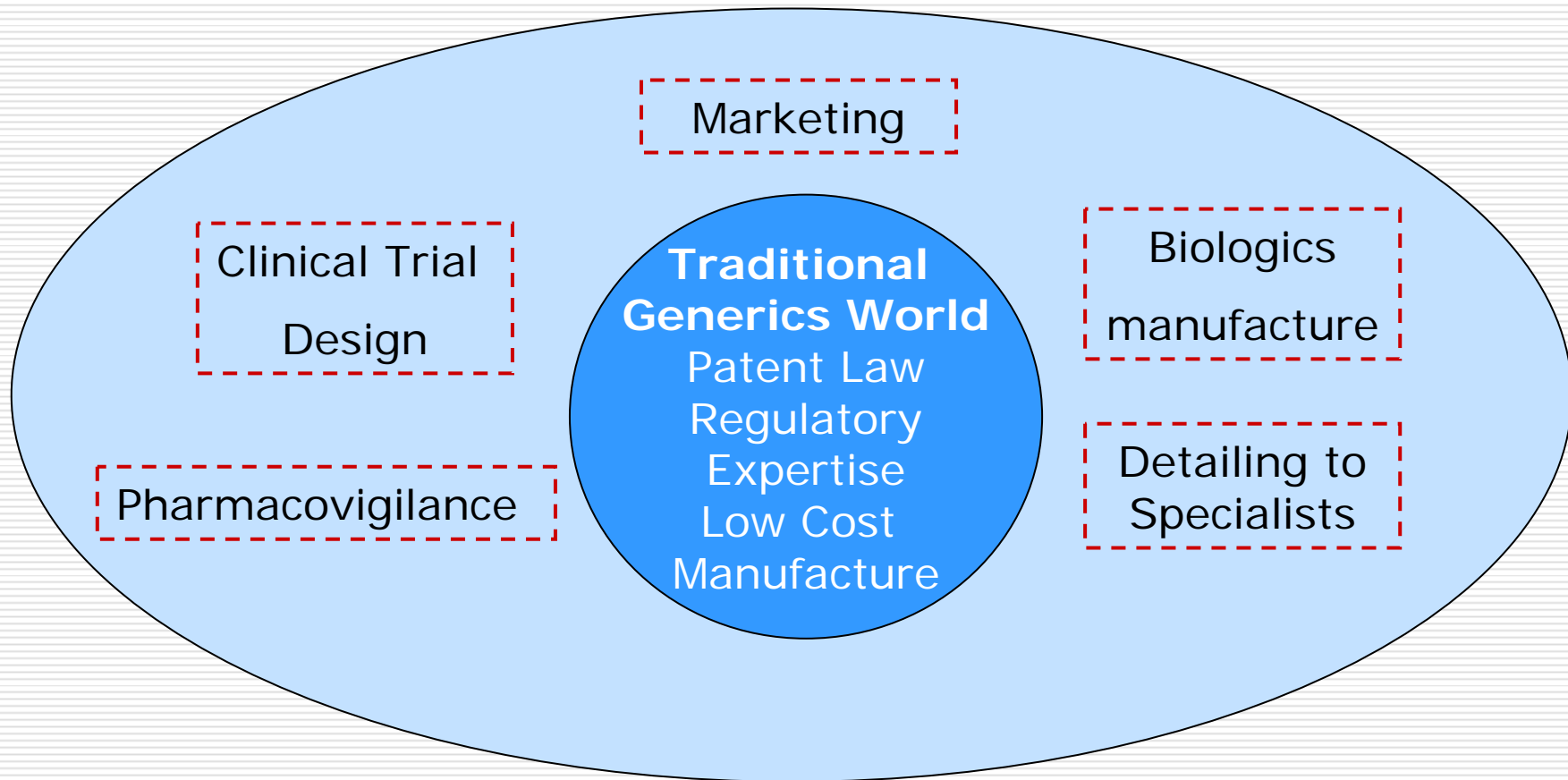
# Sustain Biogenerics Market

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- ✓ Developing a specific bio-generic regulatory framework.
- ✓ With the introduction of TRIPS agreement from January 1, 2005, Indian bio-generic companies should not concentrate on generating mere copies of the existing drugs, but try to improve manufacturing procedures, which may themselves bring new patents.
- ✓ Modifying the patent framework to suit the bio-generic products.
- ✓ Improving the approaches of generic suppliers from directly copying the drugs to generating novel targets (especially, applicable to bio-generic companies in Indian and other developing countries).
- ✓ Policies from the originators
- ✓ Customer receptivity towards biogeneric products

# Core competencies that biosimilar companies need to survive

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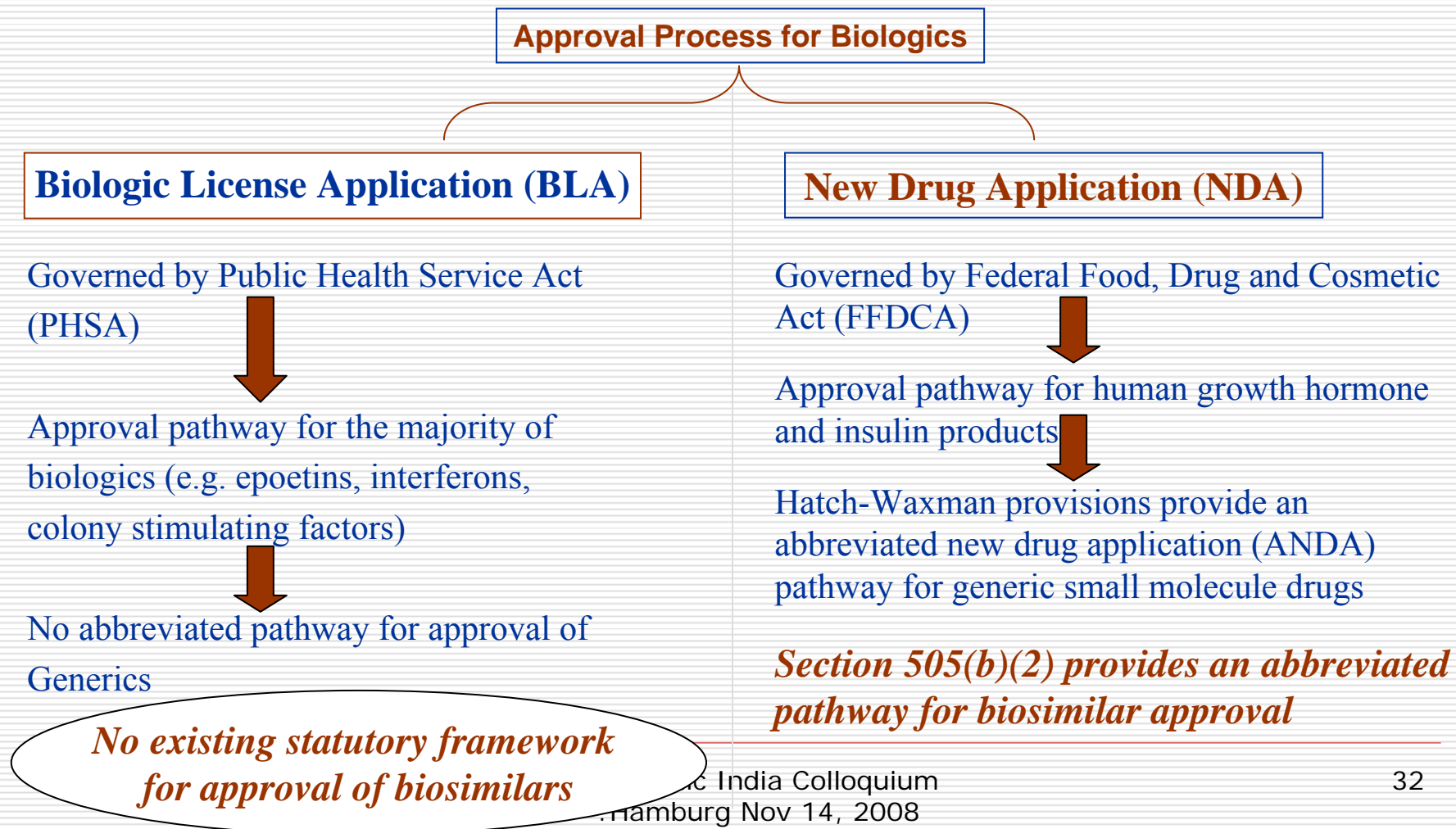
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# Biogenerics -Regulatory

**EU has guidelines in place for approval of biosimilars, US and Japan lag behind in the process.**

# US Approval Process for Biologics

- There are two distinct regulatory pathways for biologics associated with a different set of barriers for approval of biosimilars.



# EU Approval Process for Biosimilars

- Europe has a unified regulatory process for approval of Biosimilar:

**European Medicines Agency (EMA)**

## **Committee for Medicinal Products for Human Use (CHMP)**

- Reviews marketing authorization applications for biologics
- Awards either a 'positive' or 'negative' opinion based on evaluation of quality, safety and efficacy measures

**EMA has authority to recommend approval of biosimilars**

## **European Commission (EC)**

- After a product receives a positive opinion, the EC will grant marketing authorization valid for the European Union

**Final decision-maker for marketing approval of biosimilars**

# Regulations on Biogenerics in India

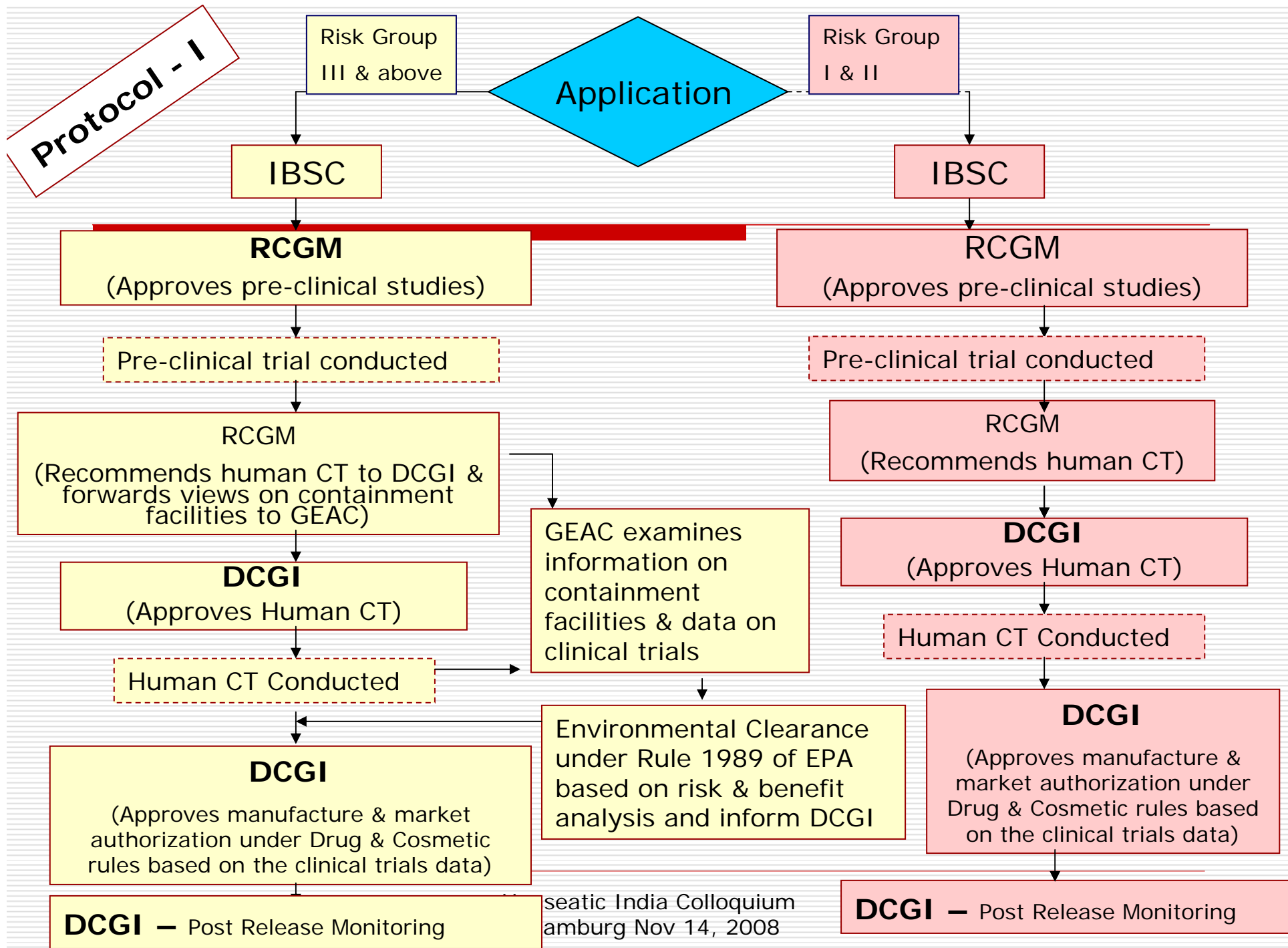
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- Institutional BioSafety Committee (IBSC)
- Review Committee on Genetic Manipulation (RCGM)
- Genetic Engineering Approval Committee (GEAC)

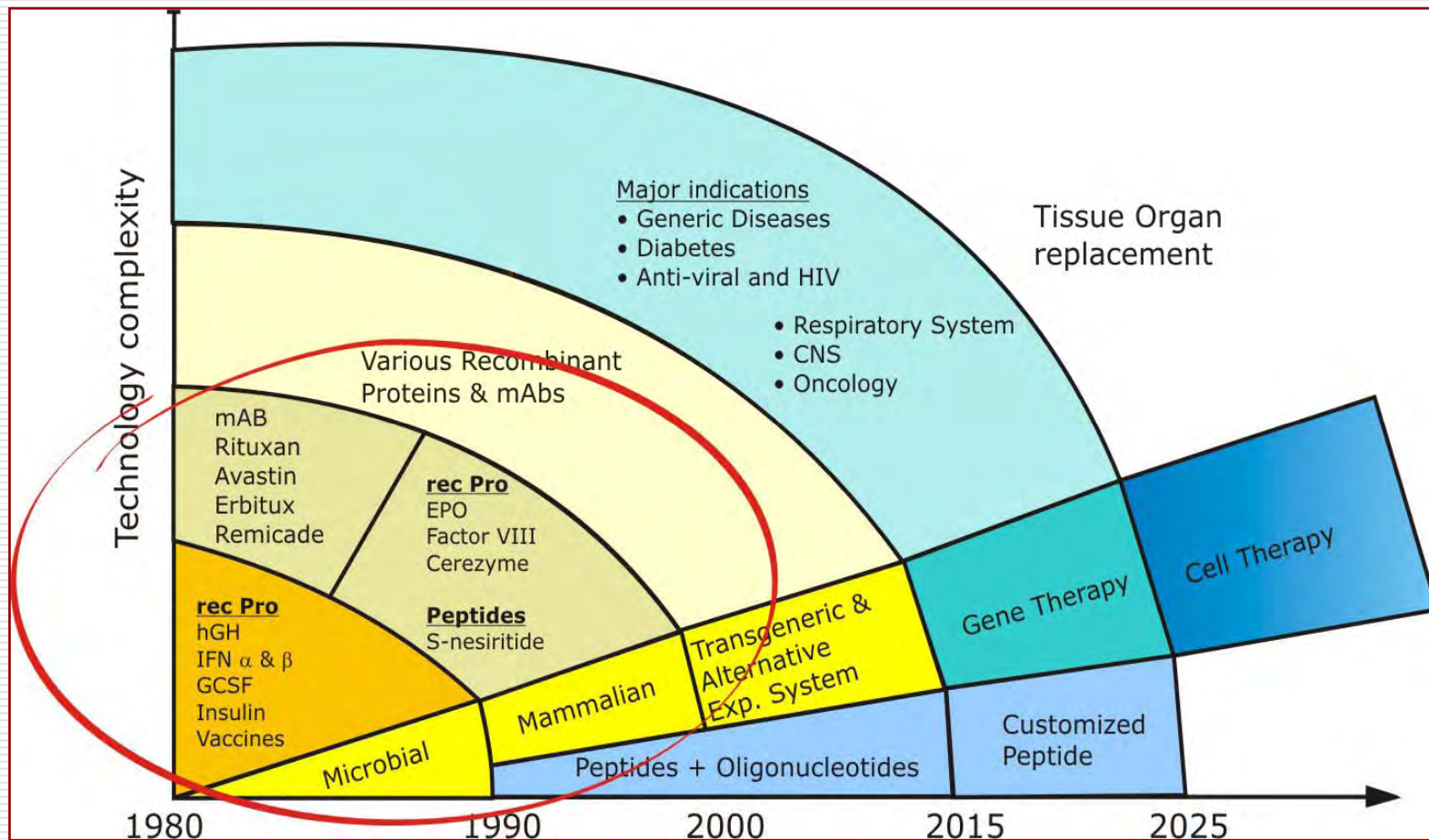
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Indigenous product development,  
manufacture & marketing of  
pharmaceutical products derived  
from LMOs but the end product is  
not an LMO.

*Report of the task force on Recombinant Pharma, 2005*



# Trends In Biopharmaceuticals



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*Thank You*



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